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Endometriosis and adenomyosis are associated with increased risk of preterm delivery and a small for gestational age child: A systematic review and meta-analysis

Running headline: Endometriosis and adenomyosis and birth

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Conflict of interest

The authors have no conflicts of interest in relation to this article.

Abstract

Introduction. The objective of this systematic review and meta-analysis was to evaluate the risk of preterm delivery and having a small for gestational age child in women with endometriosis and adenomyosis compared to women without these two diseases. *Material and methods.* Studies on endometriosis or adenomyosis and risk of preterm delivery and/or small for gestational age were included. The systematic search was conducted for all published articles in PubMed and Embase published from 1950 to 2017 using specific search terms. After duplicates were removed, two authors independently reviewed all studies, initially based on title, and subsequently, based on abstract. Studies considered relevant were read in full text by both reviewers to identify if studies met the inclusion criteria. *Results.* The searched resulted 21 studies on a total of 2 517 516 women meeting the inclusion criteria. Women with endometriosis had an increased odds of preterm delivery (OR: 1.47, 95% CI; 1.28-1.69) and small for gestational age (OR 1.26, 95% CI; 1.04-1.549). Compared with endometriosis, adenomyosis implied an even higher odds of both preterm delivery (OR: 3.09, 95% CI; 1.88-5.09) and small for gestational age (OR: 3.23, 95% CI; 1.71-6.09) as well. *Conclusions.* Women with endometriosis or adenomyosis had a higher odds of preterm delivery and having a child that was small for gestational age compared to women without endometriosis or adenomyosis. The odds of both adverse birth outcomes was highest among women with adenomyosis. The results suggest a closer prenatal monitoring among pregnant women with endometriosis or adenomyosis.

Key words

Endometriosis, adenomyosis, preterm delivery, preterm birth, small for gestational age, birthweight, premature

Abbreviations:

ART, Assisted Reproductive Technology;

BMI, Body Mass Index;

CI, confidence interval;

IVF-ICSI, In Vitro Fertilization-Intracytoplasmic Sperm Injection;

NOS, Newcastle-Ottawa Scale;

OR, odds ratio;

PTB, preterm birth;

SGA, small for gestational age

Key Message

The existing literature exploring whether women with endometriosis and adenomyosis have a higher odds of adverse birth outcomes is sparse and inconclusive. This systematic review and meta-analyses find that endometriosis and adenomyosis are associated with adverse birth outcomes. More attention to this is needed and future research is warranted on whether to recommend closer prenatal monitoring in pregnant women with endometriosis and adenomyosis.

Introduction

Endometriosis and adenomyosis are related chronic diseases affecting women in the reproductive age. Endometriosis is characterized by the presence of endometrium-like tissue outside the uterus, typically in the pouch of Douglas, whereas adenomyosis is defined by ingrowth of the endometrium into the myometrium (1). The two diseases coexist in some but not all patients (2) and both diseases may be linked to structural and functional changes in the submucosal proportion of the myometrium, the so-called junctional zone (1). In endometriosis, junctional zone dysfunction may afford the retrograde menstruation thought to be an initial step in the pathogenesis (3), while more pronounced junctional zone changes are seen in adenomyosis (1).

The prevalences are not clearly established. In the general population, endometriosis is estimated to affect approximately 10%, and up to 35-50% of infertile women are affected (4, 5). The prevalence of adenomyosis is even more uncertain with reports varying from 5-35% in the general population (5).

Although the two disesases share symptoms of pelvic pain and abnormal menstrual bleeding, there are important differences. Adenomyosis is defined as endometrial cells in the myometrium accompanied

by muscular hyperplasia, hypertrophy and fibrosis (2); the ectopic endometrial-like tissue can be widespread in women with endometriosis (4). Furthermore, endometriosis is most common among young women and is known to affect fertility, whereas infertility is less common in women with adenomyosis (2, 4-7). Nevertheless, as more and more women postpone their first pregnancy, endometriosis and adenomyosis increasingly affect fertility and pregnancy outcomes.

In recent years, there has been a growing focus on potential adverse pregnancy outcomes among women suffering from endometriosis or adenomyosis, and associations with obstetrical complications have been suggested such as miscarriages, late pregnancy complications, preterm delivery and having a child that is small for gestational age (SGA) (8). Several studies have investigated whether women with endometriosis and adenomyosis have a higher risk of having a child born preterm or SGA, but results have pointed in opposite directions (9-29).

A recent meta-analysis found that women with endometriosis have a higher risk of preterm delivery and SGA (30); however, they did not evaluate adenomyosis. It has been suggested that both endometriosis and adenomyosis could be associated to obstetrical complications (8), and speculations whether adenomyosis poses a larger threat to the pregnancy exist. Thus, keeping the suggested etiological associations between the two diseases in mind, it is important to study available data to assess whether the risk of preterm delivery and SGA in women with adenomyosis is as high as or even higher than in women with endometriosis. The main objective of this systematic review and meta-analysis was therefore to reassess the association between endometriosis and the risk of preterm delivery and SGA as well as to investigate whether women with adenomyosis have a higher risk of preterm delivery and SGA.

Material and Methods

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines (31).

Information sources

A systematic computerised literature search of articles published from 1950 to October 2017 was conducted for all published articles in the databases PubMed and Embase. In PubMed, the complete search words entered were: ((("Infant, Low Birth Weight"[Mesh] OR "Infant, Premature"[Mesh]) OR "Birth Weight"[Mesh]) OR preterm) OR premature) OR sga) OR "small for gestational")) AND ((endometriosis) OR adenomyosis). The corresponding search in Embase was: 'endometriosis'/exp OR endometriosis OR 'adenomyosis'/exp OR adenomyosis AND 'low birth weight'/exp OR 'prematurity'/exp OR 'birth weight'/exp OR 'Immature and premature labour'/exp OR 'small for date infant'/exp. References were collected using EndNote. No restrictions to study design and language were listed in the initial search. Furthermore, the reference list of the eligible studies was screened for additional relevant articles.

Study selection and data extraction

Eligibility criteria

Inclusion criteria were English language studies, epidemiological observational studies and studies investigating the associations between endometriosis or adenomyosis and the outcomes preterm delivery and/or SGA. Preterm delivery was defined as live birth < 37 weeks of gestation and SGA was defined as birthweight < 10^{th} percentile for gestational age.

Exclusion criteria were meta-analyses, case reports and studies with lack of relevance or insufficient data reporting. Lack of relevance included studies where results for women with endometriosis or adenomyosis were not compared to results for women without endometriosis or adenomyosis. Studies were excluded from the final meta-analysis if the associations were not reported as crude or adjusted odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI) or if the authors had not provided data that could be used to calculate crude OR with 95% CI.

Screening of studies

In the screening of relevant studies, duplicates were removed prior to abstract screening. Two authors (MRB, LHA) independently reviewed all studies and any discrepancies were resolved by consensus. First, all studies identified in the initial search were reviewed based on the title and subsequently, based on the abstract. Studies considered relevant based on titles and abstracts were read in full text by two of the authors (MRB, LHA) to identify papers that met the inclusion criteria.

The corresponding authors of three studies were contacted with questions concerning the composition of the study population (one paper), and the precise definition of preterm delivery (two papers). Based on their answers, one study was continuously included (14), another study was excluded as the outcome was threatened premature delivery (32), and the third study on preterm delivery was excluded as it only assessed preterm delivery < 34 weeks of gestation, and their results on SGA were included (9).

Assessment of risk of bias

To assess the quality of the studies included, we used the Newcastle-Ottawa Quality Assessment Scale (NOS) in which studies are scored individually between zero and nine, based upon an evaluation of selection and comparability of the study groups as well as the ascertainment of exposure and outcome (33). Two authors (MRB, LHA) independently evaluated the quality of each included study using the NOS. If disagreement between the assessed score of a study occurred, the reviewers discussed and evaluated the study to reach agreement. If necessary, a third reviewer was consulted (CHR).

Statistical analyses

Most studies stated crude or adjusted OR with 95% CI. In studies providing both crude and adjusted OR, we used the adjusted OR. In the studies that did not state the OR with 95% CI, the statistical tool, EpiBasic was applied to calculate crude OR with 95% CI on the basis of the data presented in the study. An independent calculation of an OR for each study based on the number of exposed and non-exposed would result in a crude OR for each study. It would otherwise not have been possible for us to perform a sub-analysis of studies with adjusted results, which we consider a better estimate of the true association between endometriosis or adenomyosis and adverse pregnancy outcomes. Furthermore, not all studies provided sufficient data to calculate an OR. Therefore, we only calculated an OR if the studies did not report an adjusted OR.

The Review Manager 5 software was used to conduct the meta-analysis (34). A random-effect inverse-variance weighted model for combining OR was used, resulting in a combined summary OR with 95% CI (35). Main analyses were performed for the association between the two exposures: endometriosis and adenomyosis and the two outcomes, preterm delivery and SGA, separately. The overall comparison was performed including several outcomes, the random effects model and the

effect measure of OR and 95% CI. With this method, OR and the lower limit of the 95% CI from each study could be inserted into the calculator function, which resulted in an upper limit of the 95% CI as well as a logarithm of OR (log(OR)) and a standard error (SE) for each study. A combined OR with 95% CI was calculated by uniting each log(OR) and associated SE. For each study, a weighted estimate was calculated using log(OR) and SE. Thus, studies with most weight were rated more important in the final estimate. The resulting upper limits of the 95% CI were not consistently identical to the upper limit for the OR stated in the studies because of small differences in the round off of numbers. Further, Review Manager 5 was used to assess the risk of publication bias based on Funnel Plots.

For endometriosis, we also performed the following sensitivity analyses: 1) We restricted the analyses to studies reporting adjusted OR and 95% CI, 2) we restricted the analyses to studies that only included singleton births and 3) we restricted the analyses to studies with a score of ≥ 8 on the Newcastle-Ottawa Quality Assessment Scale. For adenomyosis, one study in the main analysis included women with untreated rectovaginal deep infiltrating endometriosis in some women also including adenomyosis (27). However, accurate information on exposure was not provided and it was not possible to discern women with rectovaginal deep infiltrating endometriosis from women with adenomyosis or whether the diseases coexisted. For that reason, the study was excluded in the sub-analyses on the association between adenomyosis and birth weight and SGA (27).

Results

Figure 1 illustrates the flowchart of studies identified in the literature search and included in the systematic review and meta-analysis. In total, 21 studies published between 2003 and 2017 on the association between endometriosis or adenomyosis and preterm delivery or SGA among a total of 2 517 516 women were included. Among all studies, 20 were cohort studies and one was a case-control study. 11 studies were from Europe, seven studies from Asia, two studies from America and one study was from Australia. Of the 21 studies, four included adenomyosis, whereas 17 studies consisted of different sub-types of endometriosis including superficial endometriosis, deep peritoneal endometriosis and endometriomata. Table 1 presents characteristics of each study included and Table 2 outlines the main results in each study of the included studies.

Endometriosis

Preterm delivery

In total, 16 studies were identified investigating the association between endometriosis and preterm delivery (10-25). The meta-analyses showed that women with endometriosis had a higher odds of preterm delivery [OR: 1.47, 95% CI; 1.28-1.69] than women without endometriosis (Figure 2A). This finding was rather consistent across the sensitivity analyses performed. First, the analysis was restricted to the 13 studies reporting adjusted ORs, and we observed an OR of 1.48 (95% CI; 1.28-1.71) (Supporting Information Figure 1). Secondly, the analysis was repeated limited to 14 studies with singleton births only and we found an OR of 1.45 (95% CI; 1.26-1.68) (Supporting Information Figure 3). Finally, assessing the quality of the included studies, analyses based on results from five studies with a NOS score of ≥ 8 were conducted and the higher odds of preterm delivery persisted [OR: 1.35, 95% CI; 1.18-1.54] (Supporting Information Figure 5). Heterogeneity (I^2 = 55%, p = 0.005) between the included studies was rather high.

A sub-analysis including one relevant conference abstract was also performed (36). This conference abstract did not state sufficient relevant data to be included in the main analysis and it was not possible to assess the quality using NOS due to sparse information. The sub-analysis on endometriosis and preterm delivery resulted in an OR of 1.46 (95% CI; 1.29-1.66) and a rather high heterogeneity (I^2 = 52 %, p = 0.006). These results did not differ considerably from the main results.

Small for gestational age

Of the total of 21 studies, 13 described the association between endometriosis and SGA (9, 10, 14-18, 20-25). The meta-analysis revealed a higher risk of having a SGA child among women with endometriosis, with an overall OR of 1.26 (95% CI; 1.04-1.54) (Figure 2B). When only including the adjusted OR, very similar results were found [OR: 1.26, 95% CI; 1.01-1.56] (Supporting Information Figure 2). When only assessing the associations among singleton births, an OR of 1.24 (95% CI; 0.99-1.56) was found (Supporting Information Figure 4). Further, five studies reached a NOS score ≥ 8 and the meta-analysis of these showed attenuated results [OR: 1.13, 95% CI; 0.88-1.46] (Supporting Information Figure 6). A rather high heterogeneity (I^2 = 72%, p < 0.0001) between studies was observed.

Funnel plots were made to depict the association between endometriosis and preterm delivery and SGA. The asymmetry in both funnel plots aroused suspicion that publication bias could exist because small studies were not published (Supporting Information Figure 9 and Supporting Information Figure 10).

Adenomyosis

Preterm delivery

A total of four studies were identified investigating the association between adenomyosis and preterm delivery (26-29). The meta-analysis revealed even higher odds of preterm delivery in pregnant women with adenomyosis compared to pregnant women without adenomyosis [OR of 3.09 (95% CI; 1.88-5.09)] (Figure 2C). The sub-analysis restricted to three studies provided similar results with only a small reduction in OR to 2.90 (95% CI; 1.59-5.28) (Supporting Information Figure 7).

A rather high heterogeneity (I^2 = 41%, p = 0.16) between the included four studies in the meta-analysis was observed.

Small for gestational age

In total, three studies evaluated the association between adenomyosis and SGA (26-28). There was a higher risk of SGA in pregnant women with adenomyosis compared to pregnant women without adenomyosis [OR: 3.23, 95% CI; 1.71-6.09] (Figure 2D). A sub-analysis restricted to two studies on adenomyosis found an OR of 3.96 (95% CI; 2.02-7.78) (Supporting Information Figure 8). A rather low heterogeneity (I^2 = 4%, p = 0.35) between the three studies included in the meta-analysis was found.

As only few studies were included on the association between adenomyosis and preterm delivery and SGA, respectively, it was not possible to perform sub-analyses as we did for endometriosis. Further, the information gained from the funnel plots was sparse and no conclusion regarding risk of publication bias could be reached (Supporting Information Figure 11 and Supporting Information Figure 12).

Overall, studies on the association between endometriosis and preterm delivery and SGA have pointed in different directions; some reported an increased risk of preterm delivery (10-19, 22-24) and having a SGA child (9, 14-18, 20, 23-25), whereas other did not support this (10, 20-22, 25). Regarding adenomyosis, all published studies found an increased risk of preterm delivery (26-29) and SGA (26-28), yet with considerable differences in the strength of the association.

Discussion

Results of the meta-analysis including 21 studies and a total of 2 517 516 women, supported our hypothesis that women with endometriosis and adenomyosis have an increased odds of preterm delivery and SGA. Women with adenomyosis had the highest odds of both preterm delivery and SGA.

Recent systematic reviews and meta-analyses found, that women with endometriosis have an increased risk of preterm delivery (30, 37) and SGA (30). To the best of our knowledge, no previous systematic reviews and meta-analyses have assessed the association between adenomyosis and adverse birth outcomes.

It has repeatedly been debated whether endometriosis and adenomyosis are in fact part of a continuum of diseases or separate entities (1, 2, 38). Studies have suggested that both diseases could develop based on a disturbed uterine peristalsis and dislocation of the basal endometrium (1, 6, 38, 39). Further endometriosis-related factors potentially involved in adverse pregnancy outcomes include reactive oxygen species formation, inflammation and progesterone resistance (40).

Preterm delivery and SGA are associated with both short-term and long-term complications for the child. Neonates born preterm or SGA have a higher short-term mortality and neonatal morbidity, including among others brain hemorrhage, temperature instability, and respiratory distress (41, 42). Long-term sequelae of preterm delivery include, depending on degree of prematurity, neurodevelopmental disability, bronchopulmonal dysplasia, and prematurity retinopathy (41, 43), as well as metabolic syndrome and cardiovascular disease in adulthood for SGA (42, 43). As preterm delivery and SGA are significant predictors for both a short-term and a long-term health of the

offspring, knowledge on whether endometriosis or adenomyosis is associated with these adverse birth outcomes has important and also clinical implications.

This study has strengths as well as limitations that may have influenced the results. It represents a large and comprehensive meta-analysis based on 21 studies with a novel focus on adenomyosis. In previous meta-analyses it was not considered whether multiple births might have affected the results. We consider this very important, as twinning is highly associated with preterm delivery or SGA. Additionally, endometriosis is associated with infertility and need for Assisted Reproductive Technology (ART), which increases the probability of multiple births. For that reason, a sub-analysis was conducted on the association between endometriosis and the risk of preterm delivery and SGA, only among singleton births. The strong association between endometriosis and delivering preterm persisted, indicating that this association is not only affected by twinning; the association between endometriosis and SGA attenuated slightly.

Conception by ART also increases the risk of SGA and preterm delivery (44). Glavind *et al.* (10) therefore stratified their birth cohort data according to use of ART, but their findings of an increased risk of both pregnancy complications in endometriosis patients remained essentially the same.

In general, limitations of meta-analyses include an increased risk of reporting bias since papers supporting strong associations are most likely to be published. Furthermore, quality of the meta-analysis depends on the internal validity of each study. In this study, two independent authors evaluated all included studies and each study was assessed with the NOS. This information was subsequently used in sub-analyses, restricted to studies with a NOS score ≥ 8, and thus a high internal validity, to assess the validity of the main results. In the sensitivity analyses, we found similar results to those reported in the main analysis, however, not for the association between endometriosis and SGA.

Another aspect that might have affected results is the quality of information on exposure and outcome. The included studies differed in their ascertainment on endometriosis and adenomyosis. Furthermore, not all studies distinguished explicitly between the two conditions. This could result in analysis of adverse birth outcomes in a mixed group. Information could be derived from medical registers, medical reports, or self-reports. Besides, information on endometriosis and adenomyosis could be derived from descriptions following surgical treatment, laparoscopy, magnetic resonance imaging or transvaginal ultrasonography. However, we are quite certain that outcomes in each study

were most likely correctly defined, as preterm delivery is defined as a live birth < 37 weeks of gestation and SGA is defined as a birthweight < 10^{th} percentile of gestational age. Further, it is a rather simple and standard task to collect information on preterm delivery and SGA. Nevertheless, it is important to keep in mind that preterm delivery and SGA are different but related outcomes with both individual and common risk factors and both short-term and long-term complications for the newborn (45). In general, studies included in this systematic review did not distinguish elective from spontaneous preterm deliveries. Furthermore, the included studies provided no detailed information on either treatment or severity of endometriosis and adenomyosis. This could complicate the comparison between studies.

Among the 21 included studies, not all were adjusted for potential confounders and there may be residual confounding. Results from the sub-analysis of studies with adjusted results were consistent for preterm delivery but slightly attenuated for SGA. For all main analyses, apart from the association between adenomyosis and SGA, heterogeneity was high, which indicates that studies were not completely comparable.

For adenomyosis, it was not possible to conduct sub-analyses as for endometriosis due to the small number of relevant studies. One study included in our meta-analysis did not distinguish women with adenomyosis from women with rectovaginal deep infiltrating endometriosis, which could give rise to bias (27). A sub-analysis was thus made excluding this study, However, this only changed the results for preterm delivery and SGA to a minor extent. Further, one of the included studies on adenomyosis included adjusted results and received a NOS score ≥8 (29), whereas the other studies did not provide adjusted results and obtained a NOS score < 8 (26-28). Lacking adjustment could result in confounding, especially considering maternal age, because adenomyosis is often seen in older women, and age could affect the association between adenomyosis and adverse pregnancy outcomes. All studies on adenomyosis presented results on singleton births, which made it possible to assess the association between adenomyosis and preterm delivery and SGA without twinning being an effect modifier. Thus, our findings on adverse birth outcomes among women with adenomyosis are strengthened as they only included singleton births.

Overall, this systematic review and meta-analyses indicated that women with endometriosis and adenomyosis are at higher risk of preterm delivery and SGA. The clinical relevance for the risk of preterm delivery in endometriosis patients is further corroborated by specific findings in two recent

studies included in our material where the study size enabled a more detailed analysis. These results showed an increased risk of very preterm (< 32 weeks of pregnancy) (10) and extremely preterm delivery (< 28 weeks of pregnancy) (9) in patients with endometriosis. Additionally, both endometriosis (4) and preterm delivery (46) are relatively frequent. Therefore, the association between endometriosis and preterm delivery shows an important risk profile since the total number of affected women may be substantial.

The meta-analysis further indicated that women with adenomyosis faced the highest risks, although the result was based on few original studies and consequently uncertain estimates with wide confidence intervals. The increased risk persisted when one study with very uncertain classification of endometriosis and adenomyosis was excluded. However, the findings for endometriosis may have been impacted by the simultaneous presence of adenomyosis as this disease is more prevalent in patients with endometriosis (47, 48). Further research with a detailed pre-pregnancy diagnosis is needed to assess the specific risk profile for the two diseases separately and in combination. Although speculative, adenomyosis could well be associated to more adverse pregnancy outcomes compared to endometriosis due to the more pronounced junctional zone changes suggested (1, 6, 38). Additionally, potential pathogenic mechanisms for both diseases include inflammation and enhanced formation of reactive oxygen species (2, 40).

Conclusion

In conclusion, this systematic review and meta-analysis including 21 studies and a total of 2 517 516 women support the hypotheses that women with endometriosis or adenomyosis have a higher risk of preterm delivery and having a SGA child. It should be noted that the risk seemed to be higher among women with adenomyosis, and future studies should seek to explore this further. This study may suggest the benefits of a closer prenatal monitoring of pregnant women suffering from endometriosis and adenomyosis to prevent adverse birth outcomes.

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Supporting Information legends

Figure S1. Endometriosis sub-analysis of adjusted OR and preterm delivery.

Figure S2. Endometriosis sub-analysis of adjusted OR and SGA.

Figure S3. Endometriosis sub-analysis of only singleton births and preterm delivery.

Figure S4. Endometriosis sub-analysis of only singleton births and SGA.

Figure S5. Endometriosis sub-analysis of NOS score of ≥ 8 and preterm delivery.

Figure S6. Endometriosis sub-analysis of NOS score of ≥ 8 and SGA.

Figure S7. Adenomyosis sub-analysis of preterm delivery - Exacoustous et al. excluded.

Figure S8. Adenomyosis sub-analysis of SGA - Exacoustous et al. excluded.

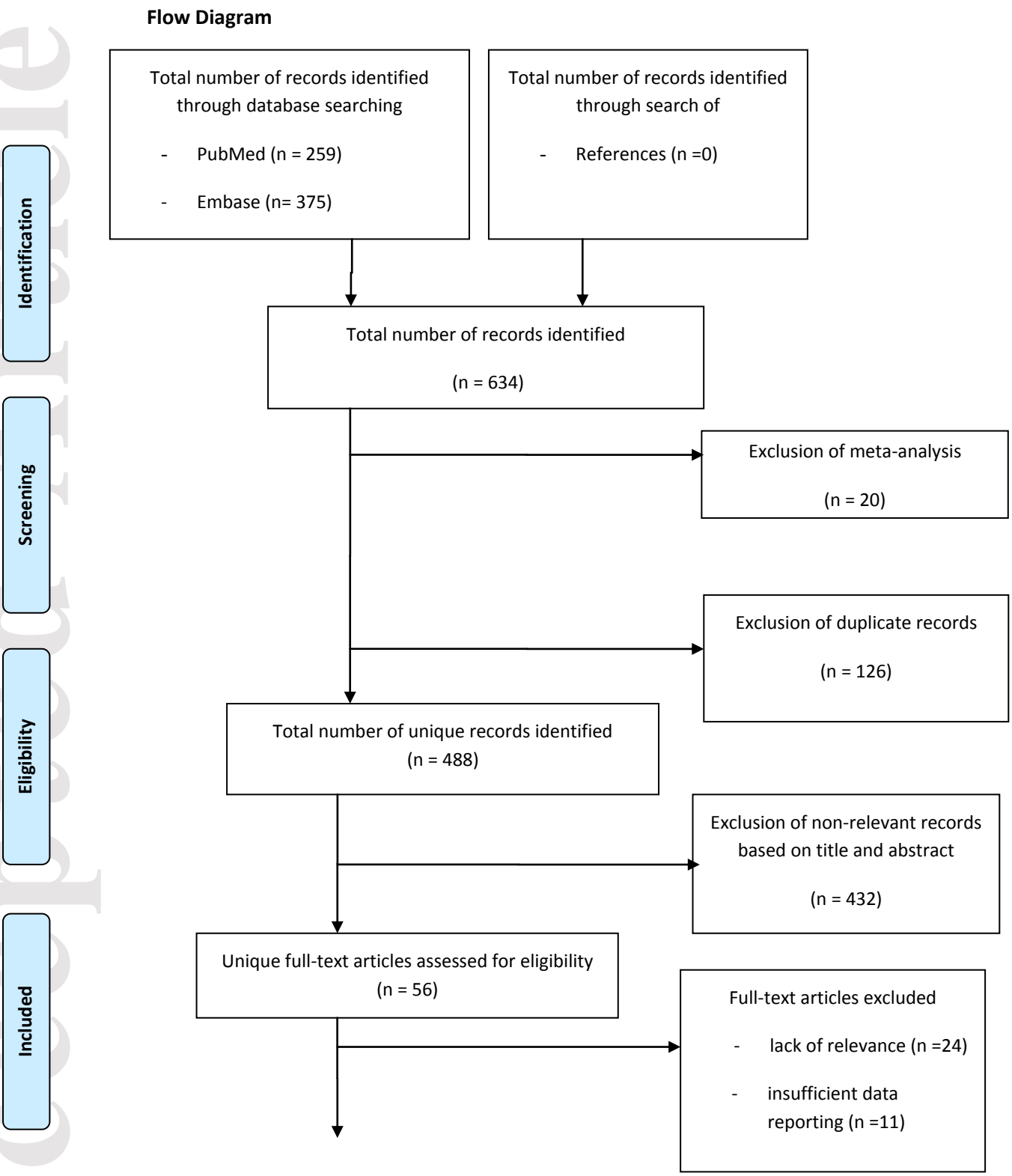
Figure S9. Funnel plot for endometriosis and preterm delivery.

Figure S10. Funnel plot for endometriosis and SGA.

Figure S11. Funnel plot for adenomyosis and preterm delivery.

Figure S12. Funnel plot for adenomyosis and SGA.

Figure 1. Flow chart. SGA: small for gestational age; n: number.



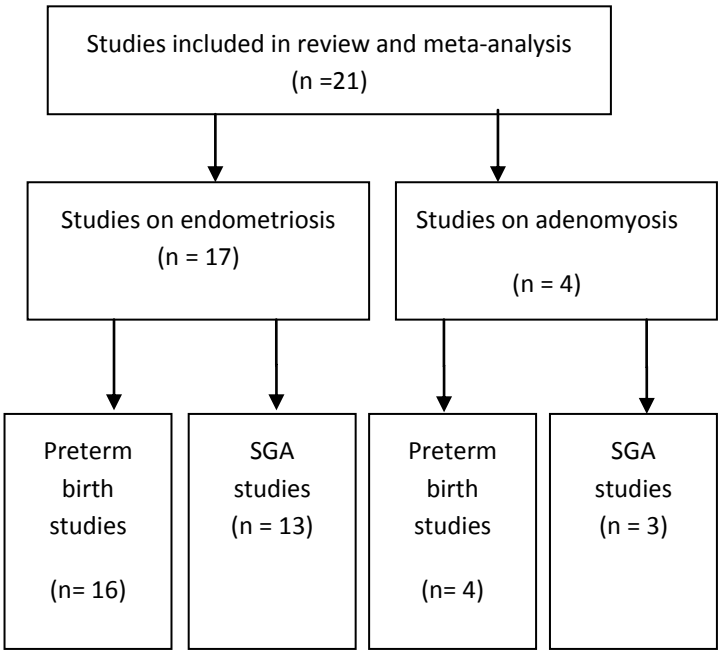


Table 1. Publications on the association between endometriosis and adenomyosis and preterm birth and small for gestational age (SGA).

Author, year	Country	Study design	Study period	Sample size	Study population	Source of exposure data	Source of outcome data	ART	Exclusion criteria	Type of lesion	NOS score
Endometriosis											
Berlac *et al*., 2017 (9)	Denmark	Cohort	1977-2014	- 627 272 women - 11 739 women with endometriosis and 19 331 deliveries	15-49 years old women in the Danish Health Register	Register data Danish National Health Register	Register data Danish Medical Birth Register	With and without ART No stratification	No exclusion criteria stated	All subtypes of endometriosis	9
Glavind *et al*., 2017 (10)	Denmark	Cohort	1989-2013	- 82 793 singleton births - 1213 women with endometriosis	Women at routine antenatal care at a department of obstetrics and gynecology	Register data Danish National Registry	Register data Aarhus Birth Cohort	With and without ART Stratification	Stillbirths	All subtypes of endometriosis	8
Li *et al.*, 2017 (11)	China	Cohort	2011-2013	- 398 women. - 98 women with endometriosis.	Nulliparous women with singleton pregnancies in a department of obstetrics and gynecology.	No information stated besides evaluation according to rASRM classification	No information stated	With and without ART Stratification	Malignancies, adenoymyosis, immune system, endocrine and cardiovascular diseases, other complications	Superficial endometriosis, deep endometriosis	7
Mannini *et al.*, 2017 (12)	Italy	Cohort	2009-2014	- 786 women - 262 women with	Women delivering at a tertiary hospital	No information stated besides previous surgical evaluation for	No information stated	With and without ART	Biochemical pregnancies, ectopic pregnancies,	Endometriomas, superficial endometriosis, deep	6

				endometriosis	in Italy	endometriosis as well as a pathological diagnosis		No stratification	missing data	endometriosis	
Saraswat *et al.*, 2017 (13)	Scotland	Cohort	1981-2010	- 14 655 women - 5375 women with endometriosis	Women in Scotland	Medical records Scottish Record Linkage	Medical records Scottish Record Linkage	With and without ART No stratification	Multiple births, suspected diagnosis of endometriosis due to symptoms but no surgical confirmation	All subtypes of endometriosis	8
Benaglia *et al.*, 2016 (14)	Italy	Cohort	2004-2009	- 478 women - 239 women with endometriosis	Women undergoing IVF at two infertility units in Italy	Medical records	Questionnaire	With ART	Uterine malformation, intramural fibroid, multiple pregnancy, pre-pregnancy DM and hypertension, previous organ transplantation, antiphospholipid syndrome, chronic renal disease, SLE	All subtypes of endometriosis	7
Fuiji *et al.*, 2016 (15)	Japan	Cohort	20000-2004	- 604 women - 92 women with endometriosis	Women achieving singleton pregnancies via ART in a	Medical records	No information stated	With ART	Spontaneous pregnancies, suspected endometriosis, endometrial	All subtypes of endometriosis	7

					department of obstetrics and gynecology				or cervical cancer, conization		
Conti *et al.*, 2015 (16)	Italy	Cohort	Not stated	- 2239 women - 316 women with endometriosis	Singleton pregnant women at five gynecologic and obstetric units	No information stated aside from pathology after surgical removal of lesions	No information stated	With and without ART Stratification	Endocrine, autoimmune and systemic diseases besides uterine disorders	Ovarian, ovarian and peritoneal, ovarian and deep, deep endometriosis	7
Lin *et al.*, 2015 (17)	China	Cohort	1995-2013	- 498 women - 249 women with endometriosis	Nulliparous women with singleton pregnancies without ART at a department of obstetrics and gynecology	No information stated besides histological confirmation at surgical procedure	No information stated	Without ART	Multipara, multiple pregnancies, ART-conception, malignancies, immune-system or cardiovascular diseases	All subtypes of endometriosis	7
Stern *et al.*, 2015 (18)	USA	Cohort	2004-2008	- 305 774 pregnancies - 996 women with endometriosis	Women with singleton and twin pregnancies resulting in live-births in Massachusetts	Register data MOSART linking from SART CORS database and PELL data system	Register data MOSART linking from SART CORS database and PELL data system	With and without ART Stratification	Multiple infertility-related diagnoses, stillbirths, < GA 20 weeks, birthweight < 350 g or > 8,165 g, < 18 years of age	All subtypes of endometriosis	8

Aris, 2014 (19)	Canada	Cohort	1997-2008	- 31 068 women - 784 women with endometriosis	Women giving birth at a university hospital centre	Medical records	Medical records	With and without ART No stratification	Non-complete medical records, multiple pregnancies	All subtypes of endometriosis	7
Mekaru *et al.*, 2014 (20)	Japan	Cohort	1995-2011	- 108 women - 49 women with endometriosis	Singleton pregnant women at University of the Ryukus Hospital, Japan	No information stated besides laparoscopic evaluation according to rASRM classification	No information stated	With and without ART, without IVF/embryo transfer No stratification	Conceived via IVF/embryo transfer, hypertension or diabetes, 41 years of age or more, multiple pregnancies	All subtypes of endometriosis	4
Benaglia *et al.*, 2012 (21)	Italy and Spain	Cohort	2005-2009	- 234 women - 78 women with endometriomas	Women with singleton pregnancies via IVF-ICSI cycles in infertility units in Italy or Spain	Medical records	Medical records and additional questionnaire through phone contact	Women with ART	Biochemical pregnancies, ectopic pregnancies and twin pregnancies	Endometriomas	8
Kuivasaari-Pirinen *et al.*, 2012 (22)	Finland	Cohort	1996-2007	- 27 125 women - 49 women with endometriosis	Singleton pregnancies at a university hospital	No information stated aside from laparoscopy and ultrasonography	Register data Hospital Birth Register and databases of Obstetrics and Fertility Outpatient Departments	With and without ART No stratification	< 22 weeks of gestation or birthweight < 500 g, pregnancies with major fetal malformations	All subtypes of endometriosis	6
Fernando *et al.*, 2009 (23)	Australia	Cohort	1991-2004	- 4387 women - 630 women with endometriosis	Women with a singleton pregnancy in Australia	Medical records and register data Perinatal Data Collection Unit	Medical records and register data Perinatal Data	With and without ART No stratification	Multiple pregnancies, repeated deliveries, no	All subtypes of endometriosis	6

						and Monash IVF database	Collection Unit and Monash IVF database		infertility-etiology, via other Victorian ART clinics		
Stephansson *et al.*, 2009 (24)	Sweden	Cohort	1992-2006	- 1 442 675 singleton births - 8922 women with endometriosis	Singleton pregnancies among women in Sweden	Register data Swedish Medical Birth Register and Swedish Patient Register	Register data Swedish Medical Birth Register	With and without ART Stratification	No exclusion criteria stated	All subtypes of endometriosis	9
Kortelahti *et al.*, 2003 (25)	Finland	Cohort	1994-20000	- 274 women - 137 women with endometriosis	Women with singleton pregnancies.	Medical records and operations notes	No information stated	With and without ART Stratification	Multiple pregnancies	All subtypes of endometriosis	6

Adenomyosis											
Hashimoto *et al.*, 2017 (26)	Japan	Cohort	2000-2004	- 294 women - 49 women with adenomyosis	Women with singleton pregnancies at three institutions in Japan	Medical records	No information stated	With and without ART Matching by ART	Multiple pregnancy, history of surgery for uterine myoma or adenomyosis, uterine malformation, fetal anomalies, delivering between 12-21 weeks of gestation	Adenomyosis	7
Exacoustos us *et al.*, 2016 (27)	Italy	Cohort	2011-2015	- 500 women. - 200 women with endometriosis.	Women delivering at the same time period in an obstetric clinic	Medical records	Questionnaire	With and without ART No stratification by ART	Endocrine, autoimmune and systemic diseases, uterine disorders	Deep endometriosis, ovarian endometriomas, adenomyosis	5
Mochimaru *et al.*, 2015 (28)	Japan	Cohort	2002-2012	- 180 women - 36 women with adenomyosis	Women delivering after 22 gestational weeks at Perinatal Center for Maternity and Neonates,	Medical records	Medical records	With and without ART No stratification by ART	Surgery for uterine myoma or adenomyosis, uterine malformation, multiple gestation,	Adenomyosis	7

					Japan				fetal anomalies		
Juang *et al*., 2007 (29)	Taiwan	Case-control study	1999-2005	- 2138 women - 35 women with adenomyosis	Singleton pregnant women at a tertiary care institution	No information stated besides diagnosis based on MRI or ultrasonography	Medical records	With and without ART No stratification by ART	Elective pregnancy-termination, intrauterine fetal death, 1st prenatal visit > 18 weeks of gestation. PTB induced by interventions, inadequate data	Adenomyosis	8

Abbreviations: ART: Assisted Reproductive Technology; DM: Diabetes Mellitus; GA: Gestational Age; IVF: In Vitro Fertilization; ICSI: Intracytoplasmic Sperm Injection; MOSART: Massachusetts Outcomes Study of Assisted Reproductive Technology; MRI: Magnetic Resonance Imaging; NOS: Newcastle-Ottawa Scale; PELL: Pregnancy to Early Life Longitudinal; PTB: Preterm Birth; rASRM: revised American Society for Reproductive Medicine; SART CORS: Society of Assisted Reproductive Technologies Clinical Outcomes Reporting System; SLE: Systemic Lupus Erythematosus

Table 2. Extracted data on the association between endometriosis and adenomyosis and preterm birth and small for gestational age (SGA).

Author, year	Outcome	Crude OR(95% CI)	Adjusted OR(95%CI)	No reported OR but stated distribution	Number of exposed vs. non-exposed	Confounder adjustment
Endometriosis						
Berlac *et al.* 2017 (9)	- PTB - SGA		- PTB: OR_A 2.7 (2.5-2.9) for < GA 34 weeks and OR_A 3.1 (2.7-3.6) for < GA 28 weeks - SGA: OR_A 1.5 (1.4-1.6)		- 11 739 exposed - 615 533 non-exposed	Smoking, BMI, ART, maternal age, calendar year, parity
Glavind *et al.*, 2017 (10)	- PTB - SGA		- PTB: OR_A 1.67 (1.37-2.05) - SGA: OR_A 1.00 (0.73-1.37)		- 1213 exposed (2.2%) - 54 616 non-exposed	Maternal age, BMI, parity, ethnicity, years of school and year
Li *et al.*, 2017 (11)	- PTB		- PTB: OR_A 1.301 (0.339-4.245)		- 75 exposed - 300 non-exposed	Age at delivery, pregnancy parity
Mannini *et al.*, 2017 (12)	- PTB			- PTB: 188 with endometriosis incl. 20 with PTB. 466 without endometriosis incl. 18 with PTB. Calculated OR_C 2.96 (1.53-5.74) for singleton spontaneous	For subgroup A with singleton spontaneous deliveries: - 188 exposed - 466 non-exposed	No adjusted factors stated

			deliveries		
Saraswat *et al.*, 2017 (13)	- PTB	- PTB: OR_A 1.26 (1.07-1.49)		- 4232 exposed - 6707 non-exposed	Maternal age, parity, socio-economic status, year of pregnancy
Benaglia *et al*., 2016 (14)	- PTB - SGA	- PTB: OR_A 1.14 (0.58-2.22)	- SGA: 239 women with endometriosis incl. 14 with SGA. 239 women without endometriosis incl. 26 with SGA. Calculated OR_C 1.36 (0.79-2.34)	- 239 exposed (50%) - 239 non-exposed	BMI, duration of infertility
Fuiji et al., 2016 (15)	- PTB -SGA	- PTB: OR_A 2.08 (1.07-3.89) - SGA: OR_A 1.43 (0.68-2.81)		- 92 exposed - 512 non-expsed	Maternal age, parity, number of transferred embryos
Conti *et al.*, 2015 (16)	- PTB - SGA	- PTB: OR_A 2.24 (1.46-3.44) - SGA: OR_A 2.72 (1.46-5.06)		- 316 exposed - 1923 non-exposed	ART and infertility
Lin *et al.*, 2015 (17)	- PTB - SGA	- PTB: OR_A 2.42 (1.05-5.57) - SGA: OR_A 1.75 (0.41-7.49)		- 249 exposed - 249 non-exposed	Maternal age
		- PTB: OR_A 1.22 (0.90-1.66) with ART.			Maternal age, race/ethnicity, education,

			OR_A 1.66 (1.26-2.18) without ART			preexisting medical conditions, plurality
Stern *et al.*, 2015 (18)	- PTB - SGA		- SGA: OR_A 1.05 (0.77-1.43) with ART. OR_A 1.08 (0.81-1.43) without ART		- 996 exposed - 304 778 non-exposed	
Aris, 2014 (19)	- PTB	- PTB: OR_C 1.15 (0.91-1.45)			- 784 exposed (2.5%) - 30 284 non-exposed	No adjusted factors stated
Mekaru *et al.*, 2014 (20)	- PTB - SGA			- PTB: 40 with endometriosis incl. 3 with PTB. 48 without endometriosis incl. 4 with PTB. Calculated OR_C 0.89 (0.19-4.24) - SGA: 40 with endometriosis incl. 1 with SGA. 48 without endometriosis incl. 1 with SGA. Calculated OR_C 1.21 (0.07-19.90)	- 40 exposed - 48 non-exposed	No adjusted factors stated
Benaglia *et al.*, 2012 (21)	- PTB - SGA		- PTB: OR_A 0.47 (0.13-1.54) - SGA: OR_A 0.56 (0.12-2.56)		- 78 exposed - 156 non-exposed	Smoking, previous PTB, baseline variables differing in the groups
Kuivasaari-Pirinen *et al.*, 2012 (22)	- PTB - SGA		- PTB: OR_A 3.25 (1.50-7.07) - SGA: OR_A 0.49 (0.15-1.59)		- 49 exposed - 27 076 non-exposed	Smoking, maternal age, parity, BMI, previous fetal death and miscarriage, chronic illness, marital status

Fernando *et al.*, 2009 (23)	- PTB - SGA	- PTB: OR_A 1.98 (1.09-3.62) for ART and ovarian endometriomata. OR_A 1.03 (0.70-1.53) for other endometriosis - SGA: OR_A 1.95 (1.06-3.60) for ART and ovarian endometriomata. OR_A 0.96 (0.68-1.38) for other endometriosis	- 630 exposed - 3757 non-exposed	- PTB: maternal age, parity, year of birth - SGA: smoking, parity, year of birth
Stephansson *et al.*, 2009 (24)	- PTB - SGA	- PTB: OR_A 1.33 (1.23-1.44) - SGA: OR_A 1.04 (0.92-1.17)	- 8922 exposed with 13 090 births - No number of non-exposed but 1 429 585 births	Smoking, maternal age, parity, years of formal education, BMI, calendar year of birth
Kortelahti *et al.*, 2003 (25)	- PTB - SGA	- PTB: OR_A 0.84 (0.38-1.88) - SGA: OR_A 1.09 (0.46-2.57)	- 137 exposed - 137 non-exposed	Maternal age
Adenomyosis				
Hashimoto *et al.*, 2017 (26)	- PTB - SGA	- PTB: OR_C 3.21 (1.2-7.2) - SGA: OR_C 3.5 (1.2-9.0)	- 49 exposed - 245 non-exposed	Not adjusted, but matched by age, parity and use of ART

Exacoustous *et al.*, 2016 (27)	- PTB - SGA		- PTB: OR_C 4.50 (1.71-11.82) - SGA: OR_C 1.19 (0.26-5.41)	- 30 exposed - 300 non-exposed	No adjusted factors stated
Mochimaru *et al.*, 2015 (28)	- PTB - SGA	- PTB: OR_C 5.0 (2.2-11.4) - SGA: OR_C 4.3 (1.8-10.3)		- 36 exposed - 144 non-exposed	No adjusted factors stated
Juang *et al.*, 2007 (29)	- PTB		- PTB: OR_A 1.96 (1.23-4.47)	- 35 exposed - 277 non-exposed	Smoking, maternal age, BMI, status of previous PTB

Abbreviations: ART: Assisted Reproductive Technology; BMI: Body Mass Index; CI: Confidence Interval; GA: Gestational Age; OR: Odds Ratio; OR_A: Adjusted Odds Ratio; OR_C: Crude Odds Ratio; PTB: Preterm Birth; SGA: Small for Gestational Age.

Figure 2A: Main analysis for endometriosis and preterm delivery

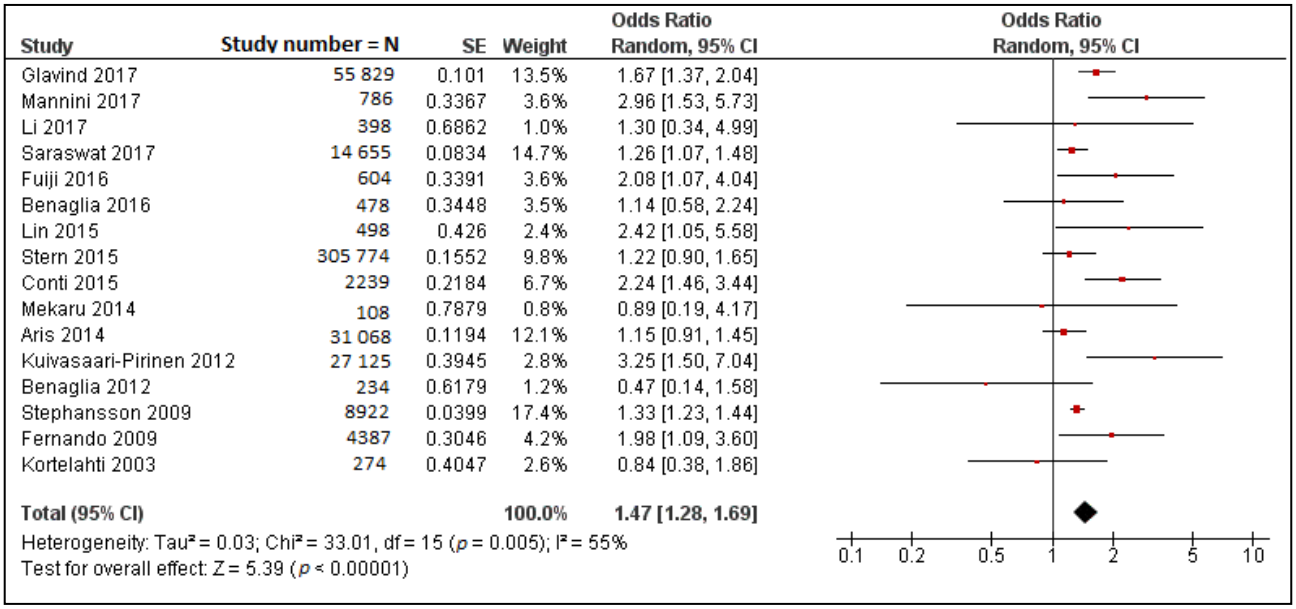


Figure 2B: Main analysis for endometriosis and small for gestational age.

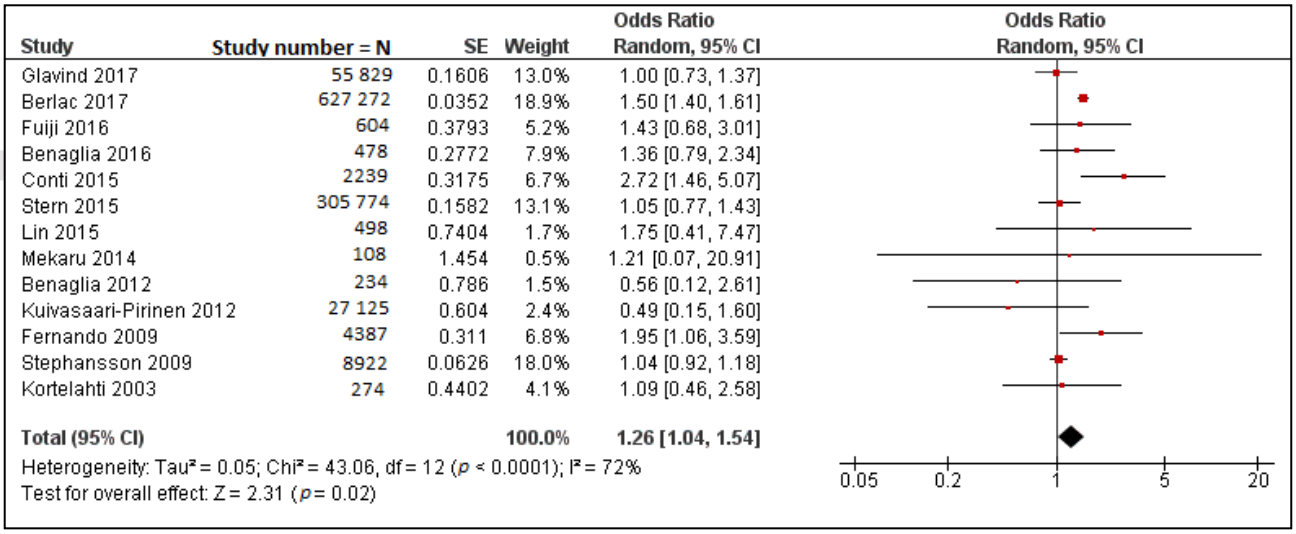


Figure 2C: Main analysis for adenomyosis and preterm delivery

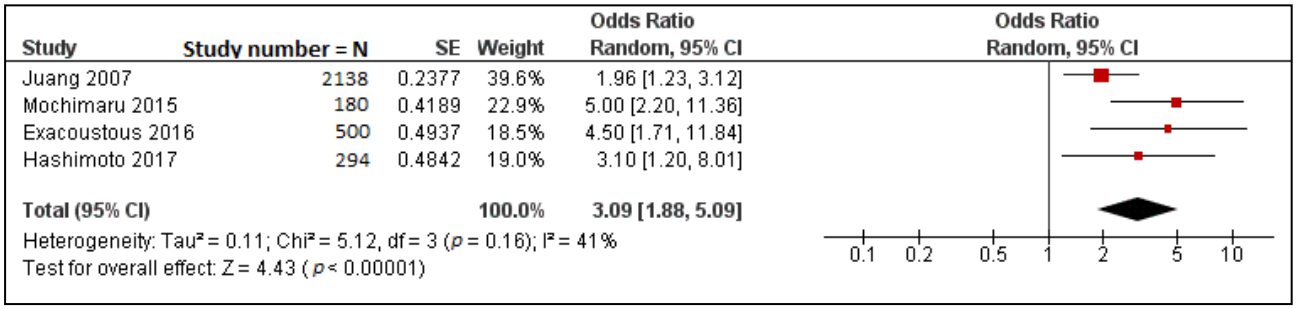


Figure 2D: Main analysis for adenomyosis and SGA